



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Johan ANDERSSON et al.

Application No.: 10/527,647

Filed: August 1, 2005

For: MANUFACTURING PROCESS FOR NO-DONATING COMPOUNDS SUCH AS NO-DONATING DICLOFENAC

Confirmation No.: 7625

Group Art Unit: 1626

Examiner: Joseph R. KOSACK

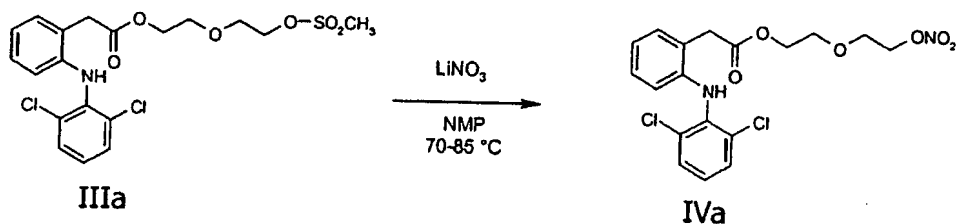
Attorney Docket No.: 026220-00064

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**DECLARATION UNDER 37 C.F.R. § 1.132**

I, Romano Rivolta, hereby declare that:

1. I am the Director of Chemistry and Formulation of NicOx S.A. ("NicOx"), located at 1681 Route des Dolines, Les Taissounières Bât HB4, Sophia Antipolis, France.
2. This Declaration presents data from an original report of Astra Zeneca of a study performed by Astra Zeneca.
3. The data demonstrates that a reaction of a sulfonate intermediate at high temperature increases the formation of impurities. The results refer to the nitrate substitution of mesylate conducted according to the following scheme:



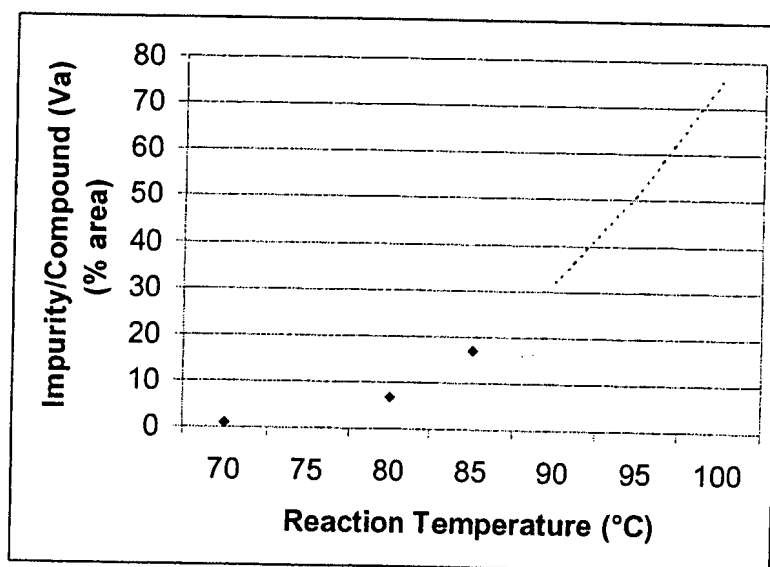
4. The data was obtained using the following materials and methods:
  - a. Three different batches of 2-{2-[(methylsulfonyl)oxy]ethoxy}ethyl{2-[(2,6-dichlorophenyl)amino]-phenyl}acetate (IIIa) were dissolved in N-methyl pyrrolidone (NMP) at three different temperatures, 70 °C, 80 °C, and 85 °C in a 5 L reactor.

- b. Each batch was then submitted to the following procedure:
- $\text{LiNO}_3$  (2.9-4.4 equivalents) was added to the dissolved starting material and the reaction was run over night.
  - The reactions were worked up by addition of water and toluene. The water was discarded, the organic phase was washed with water, and then toluene was distilled off under reduced pressure.
  - The product 2-{2-[2-(nitroxy)ethoxy]ethoxy}ethyl{2-[(2,6-dichlorophenyl)amino]-phenyl}acetate (IVa) was collected and the purity of the product was analyzed by HPLC.
5. Table 1 and Figure 1 disclose the percent conversion and the amount of impurity (Va) for the nitrate substitution of mesylate conducted according to the scheme above at three different reaction temperatures.

Table 1

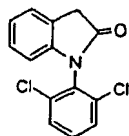
Batch (°C)	Conversion (%)	Impurity/Compound (Va) (% area)
70	98.5	0.91
80	99.4	6.79
85	99.0	16.9

Figure 1



\*projection after 85°C assumes a quadratic projection

6. Table 1 discloses that in the batch run at 85°C, impurity (Va) was formed in an amount of 16.9% area. In contrast, in the batch run at 80°C, the amount of by product was lower (6.79% area) and the batch conducted at 70°C gave even lower formation of the impurity (Va) (0.91% area).

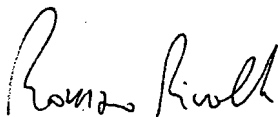


(Va)

7. Figure 1 depicts the impurity (Va) increases with increased reaction temperature. As depicted in the Figure, I would expect this trend to continue above a reaction temperature of 90°C to produce an unacceptable amount of impurities.
8. In preliminary small scale (1g) experiments, the increase of impurity (Va) was not detected. Only during the scale up to a larger 5L reactor was the increase of impurity (Va) detected, as demonstrated above.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent(s) issuing therefrom.

Date: 06 Nov 2002

  
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Romano Rivolta